in a normal subject was 0.71. This is to be contrasted with the low ratios seen in subjects with congestive heart failure, cirrhosis of the liver and orthostatic hypotension(10-12).

Summary. The day-to-night ratio of urinary chloride excretion has been determined for each of 41 normal subjects and has been calculated for 28 subjects reported in other papers. No restrictions of diet or activity were imposed. In the great majority of the subjects more chloride was excreted/hour during the up-and-about period than during the period of recumbency. This was true regardless of the amount of chloride excreted/24 hours.

1. Kleitman, N., *Am. J. Physiol.*, 1923, v66, 67.
2. Simpson, G. E., *J. Biol. Chem.*, 1926, v67, 505.
3. ———, *ibid.*, 1929, v84, 393.
4. Norn, M., *Skandin. Arch. f. Physiol.*, 1929, 55, 184.
5. Manchester, R. C., *J. Clin. Invest.*, 1933, v12, 995.
6. Stanbury, S. W., and Thomson, A. E., *Sci.*, 1951, v110, 267.
7. Mills, J. N., *ibid.*, 1951, v113, 528.
8. Campbell, J. A., and Webster, T. A., *Biochem. J.*, 1921, v15, 660.
9. Goldman, R., *J. Clin. Invest.*, 1951, v30, 642.
10. Bachman, D. M., and Youmans, W. B., *Circulation*, 1953, v7, 413.
11. Campbell, J. A., and Webster, T. A., *Biochem. J*, 1922, v16, 106.
12. Goldman, R., *J. Clin. Invest.*, 1951, v30, 1191.
13. Simpson, G. E., *J. Biol. Chem.*, 1924, v59, 107.
14. Hare, R. S., PROC. SOC. EXP. BIOL. AND MED., 1950, v78, 148.

Received May 20, 1957. P.S.E.B.M., 1957, v95.

Mechanism of Reflex Bradycardia which Follows Sudden Closure of an Arteriovenous Fistula.* (23328)

DONAL M. BILLIG† AND OSCAR W. SHADLE (Introduced by H. C. Lawson)
Department of Physiology, University of Louisville School of Medicine, Louisville, Ky.

The bradycardia which follows sudden closure of an arteriovenous fistula was first described by Nicoladoni(1), and independently by Branham(2). There have since been numerous attempts to explain the mechanism of this response. Carotid-aortic pressoreceptors(3), pressoreceptors of the right atrio-caval junction(4), and reflexes arising in the vessels at the site of the fistula(5) have all been discussed as possible sites of origin of the reflex bradycardia. Lewis and Drury (6) showed that atropine will abolish the bradycardia, and concluded that the efferent limb of the reflex is the vagus. This work was later confirmed by Kramer and Kahn(7). The purpose of this report is to describe the afferent limb of the reflex and to define the mechanism which initiates the reflex bradycardia.

Methods. Dogs, weighing 11 to 27 kg, were premedicated with 1-2 mg/kg of morphine sulfate, and anesthetized with 70-90 mg/kg of chloralose, intravenously. Heparin, 5 mg/kg, and Manuronate, 20 mg/kg, were used as anticoagulants. Heart rates were measured from electrocardiograms recorded on a Sanborn visocardiette, or in some dogs from systemic pressure pulse tracings recorded by a strain gauge or Gregg manometer. Systemic arterial pressure was measured through a brachial artery cannula, and in some experiments right atrial pressure was measured through a catheter passed into the atrium by way of the jugular vein. The carotid sinuses were denervated either by adventitial stripping and phenol painting, or by complete extirpation. The aortic arch was denervated according to a modification of the method of Comroe(8). The left vagus nerve was cut high in the neck, and all branches running medially and laterally from the right main vagal trunk were cut down to the level of the aortic arch, leaving the right main

* Supported in part by grant from Louisville and Kentucky Heart Assn.

† Louisville Heart Assn. Student Research Scholar.

TABLE I. Effect of Sudden Closure of an Arteriovenous Fistula on Heart Rate of 11 Dogs.

Before denervation		After denervation		
Control	Close	Control	Close	Remarks
194	164	210	214	Closed chest animal. Carotid sinus denervation only.
168	144	173	174	*Idem*
108	87	271	267	"
167	138	246	200	"
57	52	189	149	"
135	113	214	216	Open chest preparation. Carotid sinus and aortic arch denervation.
95	90	103	105	*Idem*
125	117	199	199	"
146	141	170	169	"
106	89	148	148	" . Aortic denervation only. Carotid sinus intact.
134	134	125	125	" . No carotid or aortic reflexes obtainable at any time.

vagal trunk with the right cardiac vagus intact. The functional integrity of the right cardiac vagus was established after the dissection by observing the effect on heart rate of electrical stimulation of the right vagus nerve high in the neck. Positive pressure respiration was used on all dogs. The arteriovenous fistula was made from brass, rubber and polyethylene tubing, arranged so as to connect both femoral arteries with a single femoral vein. The tubing connecting the arteries to the vein was manually closed with a hemostat. The carotid sinuses were stimulated by manual compression. Aortic arch compression could be done only in open chest dogs, where partial mobilization of the aortic arch had been accomplished by dissection of the right vagus. Pressure on the arch was made by means of long rubber-coated hemostats inserted through the thoracotomy incision.

Results. Fig. 1 is a segment of a record showing the typical response of the cardiovascular system to sudden closure of an arteriovenous fistula (Nicoladoni-Branham sign). The initial response is an instantaneous elevation of systolic and diastolic arterial pressures, accompanied by a bradycardia starting 2 to 4 beats later. These changes occur in the absence of any change in mean central venous pressure. Following marked initial slowing, the heart rate then tends to return toward its control value, and may fluctuate about a mean as a damped sine wave, which reciprocally follows similar waves in arterial pressure. Because of this secondary rise in heart rate, average values for heart rate over an interval of time may not give a true picture of the immediate effect of the sudden closure of a fistula.

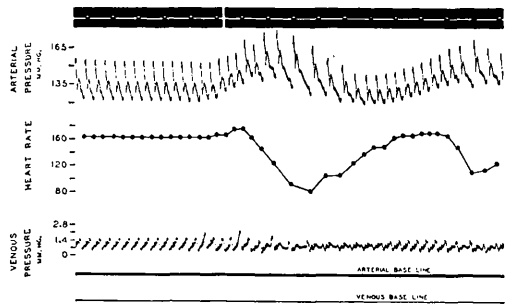

FIG. 1. Response in arterial pressure, heart rate (calculated), and venous pressure in right atrium to sudden closure of an arteriovenous fistula. Time in seconds, and instant of closure, above.

The results of all the experiments are presented in Table I. The heart rates in the Table are the average of 10 beats prior to closure (control), and 10 beats immediately following closure (close) of the fistula. The first 5 animals show the effect of carotid sinus denervation alone on the bradycardiac response. It can be seen that simple carotid sinus denervation abolished the bradycardia in 2 animals and had no effect in 2 other animals. In dog 3, the small residual change in heart rate (271-267) is probably not significant at this high rate. Because of this residual bradycardia in 2 animals with carotid sinus denervation, in the next 4 animals both the carotid sinuses and aortic arch were denervated. As indicated in the Table, this procedure completely abolished the brady-

cardia. In dog 10, aortic arch denervation alone was successful in abolishing the afferent limb of the reflex, suggesting that either of these pressor areas may predominate in an individual animal. In dog 11 no reflex bradycardia, either from closure of the fistula or from compression of the carotid sinuses or aortic arch, could ever be obtained.

Discussion. Lewis and Drury(6) were the first to suggest that sudden closure of an arteriovenous fistula increased peripheral resistance, and that the bradycardia was a response to the increased arterial pressure, which invoked Marey's Law. Nickerson, Elkin and Warren(3) studied human subjects with arteriovenous fistulae, observed the same results as Lewis and Drury, and concluded that the bradycardia was initiated via the carotid-aortic pressoreceptors. Our data give experimental confirmation to the supposition that the afferent limb of this reflex bradycardia arises from the arterial pressoreceptors. After complete denervation, closure of a fistula causes the usual changes in arterial pressure, without the bradycardia.

In some animals the bradycardia was abolished by carotid sinus denervation alone, the aortic arch receptors remaining intact, while in another dog just the reverse was found. This indicates that in an individual dog either of the pressoreceptor areas may predominate, or that they may both be receptive. This variability in the relative predominance of two homologous receptor areas has been shown to exist for the aortic and carotid chemoreceptors(8).

The "rebound effect" in arterial pressure and heart rate which follows quick closure of a fistula (Fig. 1) has been shown previously by Van Loo and Heringman(4). The same type of response to rapid arterial pressure changes has been demonstrated by Guyton and Harris(9), who abolished these waves by carotid-aortic pressoreceptor denervation. This "rebound effect" was abolished by denervation of the pressoreceptor areas in our work, offering further evidence that the afferent limb of the bradycardiac response is from the carotid sinuses and aortic arch receptors.

Conclusions. 1. The receptors for the reflex bradycardia which follows sudden closure of an arteriovenous fistula, are the pressoreceptors of the arterial side of the circulation, the carotid sinuses and aortic arch. 2. In some animals the carotid sinuses are the predominant arterial pressoreceptors, and in others the aortic arch is predominant.

1. Nicoladoni, C., *Arch. f. Klin. Chir.,* 1875, v18, 252.

2. Branham, H. H., *Internat. J. Surg.,* 1890, v3, 250.

3. Nickerson, J. L., Elkin, D. C., and Warren, J. V., *J. Clin. Invest.,* 1951, v30, 215.

4. Van Loo, A., and Heringman, E. C., *Am. J. Physiol.,* 1949, v158, 103.

5. Gerlach, F., and Harke, V., *Klin. Wchnschr.,* 1924, v3, 980.

6. Lewis, T., and Drury, A. N., *Heart,* 1923, v10, 301.

7. Kramer, M. L., and Kahn, J. W., *Arch. Int. Med.,* 1946, v78, 24.

8. Comroe, J. H., *Am. J. Physiol.,* 1939, v127, 176.

9. Guyton, A. C., and Harris, J. W., *ibid.,* 1951, v165, 158.

Received May 23, 1957. P.S.E.B.M., 1957, v95.